Economic Costs of Rotavirus Gastroenteritis and Cost-Effectiveness of Vaccination in Developing Countries

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Abstract

Background. Rotavirus is the leading cause of severe gastroenteritis in children worldwide. We evaluated the economic burden of rotavirus and the cost-effectiveness of vaccination from the health care perspective.
Methods. Estimates were based on existing epidemiological data, cost estimates, vaccine coverage, and efficacy data, as well as hypothetical vaccine prices. Outcome measures included health care and societal costs of rotavirus and benefits and incremental cost-effectiveness ratio of vaccination. Sensitivity analyses evaluated the impact of estimate uncertainty.
Results. Treatment costs increased with income level, and health burden decreased; however, burden varied across regions. On the basis of current vaccination coverage and timing, rotavirus vaccination would annually prevent 228,000 deaths, 13.7 million hospital visits, and 8.7 million disability-adjusted life-years, saving $188 million in treatment costs and $243 million in societal costs. At $5 per dose, the incremental cost-effectiveness ratio in low-, lower-middle–, and upper-middle–income countries was $88, $291, and $329 per disability-adjusted life-year averted, respectively, and $3,015, $9,951 and $11,296 per life saved, respectively. Vaccination would prevent 45% of deaths and 58% of associated medical visits and costs.
Conclusions. Vaccination is a cost-effective strategy to reduce the health and economic burden of rotavirus. The cost-effectiveness of vaccination depends mostly on vaccine price and reaching children at highest risk ofmortality

Richard D. Rheingans, Lynn Antil, Robert Dreibelbis, Laura Jean Podewils, Joseph S. Bresee,and Umesh D. Parashar (2009) "Economic Costs of Rotavirus Gastroenteritis and Cost-Effectiveness of Vaccination in Developing Countries" *Journal of Infectious Diseases* Issue 200 pp. S16-S27 Version of Record Available From www.oxfordjournals.org

Rotavirus is the most common cause of severe gastroenteritis in young children worldwide and is estimated to cause >500,000 deaths, >2 million hospitalizations, and >25 million clinic visits each year among children <5 years of age [1]. In addition to the pain and suffering in children, these rotavirus-associated events result in increased medical expenses, lost productivity, and other costs to society and families. Two effective rotavirus vaccines have recently become available and could significantly reduce this burden [2, 3].

Decisions to adopt vaccination programs depend on multiple factors, including the health burden, vaccine effectiveness, and cost-effectiveness of a vaccination program. Although economic analyses have played a central role in the consideration of new childhood vaccines for industrialized countries, decisions to introduce new vaccines in developing countries have traditionally been driven by data on disease burden. However, with

Potential conflicts of interest: none reported.

Financial support: Global Alliance for Vaccines and Immunization (GAVI) and The Vaccine Fund (GAV1142-01-07240-SPS). The model used in this analysis was based on a model developed with the support of GSK Biologicals.

Supplement sponsorship: This article was published as part of a supplement entitled "Global Rotavirus Surveillance: Preparing for the Introduction of Rotavirus Vaccines," which was prepared as a project of the Rotavirus Vaccine Program, a partnership between PATH, the World Health Organization, and the US Centers for Disease Control and Prevention, and was funded in full or in part by the GAVI Alliance.

The views expressed by the authors do not necessarily reflect the views of the Rotavirus Vaccine Program, the GAVI Alliance, or the Vaccine Fund. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of Centers for Disease Control and Prevention.

Presented in part: World Health Organization Meeting on Economic Burden of Rotavirus Disease and Cost-Effectiveness of Rotavirus Vaccination, Geneva, 2006.

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Table 1. Input Variables and Ranges: General Parameters

Parameter	Baseline estimate (range)	Distribution for uncertainty analysis	Reference(s)
Health			
5-year risk of hospitalization for rotavirus infection			
Low income	0.016 (0.012–0.02)	Triangular	[8]
Lower-middle income	0.020 (0.015–0.025)	Triangular	[8]
Upper-middle income	0.029 (0.022–0.036)	Triangular	[9–14]
5-year risk of an outpatient visit for rotavirus infection			
Low income	0.202 (0.152–0.252)	Triangular	[8]
Lower-middle income	0.202 (0.152–0.252)	Triangular	[8]
Upper-middle income	0.233 (0.175–0.291)	Triangular	[8]
Hospital length of stay, days	4.0 (3–5)	Triangular	[9, 11, 14, 15–32]
Vaccine efficacy			
Severe rotavirus GE resulting in hospitalization or death	0.85 (0.70–0.94)	Log normal	[33]
Moderate rotavirus GE resulting in outpatient visit	0.78 (0.58–0.89)	Log normal	[34, 33]
Effectiveness reduction with 1 dose	0.5 (0.25–0.75)	Uniform	Authors' assumption
Effectiveness reduction in subsequent seasons for mild cases	0.04 (0–0.25)	Uniform	[35]

NOTE. Ranges for triangular and uniform distributions are minimum and maximum values, and ranges for log-normal distributions are 2.5th and 97.5th percentiles. GE, gastroenteritis.

the increased availability of international resources to improve childhood vaccination in developing countries, cost-effectiveness analyses are increasingly used by policy-makers to allocate resources among many competing priority interventions. Economic evaluations of vaccines can assess whether they are cost saving (averted costs are greater than the intervention) and their cost-effectiveness (comparing net costs with the health gains).

In the present study, we examined the economic burden of rotavirus and the cost-effectiveness of vaccination in low- and middle-income countries, which account for the vast majority of the global burden of severe rotavirus gastroenteritis [1]. The current analysis assessed the costs and effects of a rotavirus vaccine, compared with current diarrheal control measures without vaccination.

METHODS

Model overview. We analyzed the economic burden of rotavirus and the cost-effectiveness of routine rotavirus vaccination of infants in low- and middle-income countries. Countries were placed into the regional groups used by the World Health Organization (WHO; African, American, eastern Mediterranean, European, Southeast Asian, and western Pacific regions) [4], and each regional group was further divided into 3 income strata (low, lower middle, and upper middle) [5]. The regional income group was the unit of analysis, and a total of 17 regional income groups were assessed. Countries included in this analysis account for ~99% of the global rotavirus mortality burden [1] and >90% of the global 2004 birth cohort [6].

A Microsoft Excel–based model was developed to estimate the health care and social costs of rotavirus gastroenteritis and the cost-effectiveness of vaccination, which has been described in detail elsewhere [7]. The model estimates health outcomes (hospitalizations, outpatient visits, and deaths) of rotavirus disease and their associated costs for an annual birth cohort [6] followed up for a 5-year period. It also estimates the disease burden and health care costs averted as the result of vaccination. The principal model inputs include epidemiological information on disease incidence, health care treatment costs, and the effectiveness and cost of vaccination (Tables 1 and 2).

The primary analysis was conducted from a health care system perspective focusing on direct medical costs from hospitalization and outpatient visits. These include the cost of diagnostic tests, medication, supplies, facilities, and personnel. Secondary analyses of economic burden were conducted from a societal perspective and included transportation costs and productivity losses of caregivers. No economic costs were included for cases resulting in death or for patients not seeking formal medical attention. The health burden of rotavirus was also estimated in terms of disability-adjusted life-years (DALYs), which quantify the years lost because of premature mortality and the years lived with disability [38]. Loss of potential productivity because of mortality was not included in the model. The model also estimated the incremental cost-effectiveness ratio (US$ per DALY averted and US$ per death averted) of rotavirus vaccination. Estimates are expressed in 2007 US dollars, and all future costs and DALY estimates are discounted at a rate of 3%.

Rotavirus-associated hospitalizations, outpatient visits, and mortality. For low-, lower-middle–, and upper-middle–in-

Table 2. Input Variables and Ranges: Region-Specific Parameters

Region, income group	Rotavirus-associated mortality rate, deaths per 1000 children <5 years of age	Hospital visit treatment cost, US$	Outpatient visit treatment cost, US$	Vaccine administration cost, US$
African				
Low	2.17	43.84	4.10	0.48
Lower-middle	0.16	47.48	4.45	0.47
Upper-middle	0.27	71.18	6.75	0.94
Americas				
Low	0.93	57.12	4.92	0.58
Lower-middle	0.27	113.23	10.79	0.67
Upper-middle	0.22	201.67	20.44	1.33
Eastern Mediterranean				
Low	1.38	67.59	7.20	0.76
Lower-middle	0.38	88.43	8.99	0.73
Upper-middle	0.13	237.68	24.09	1.46
Europe				
Low	0.73	71.52	6.35	1.30
Lower-middle	0.25	102.82	9.68	1.23
Upper-middle	0.001	174.55	19.52	2.46
Southeast Asia				
Low	0.95	30.47	2.31	0.37
Lower-middle	0.26	58.27	5.02	0.25
Western Pacific				
Low	0.69	55.82	4.56	0.27
Lower-middle	0.32	78.44	6.70	0.38
Upper-middle	0.06	103.78	9.12	0.77

NOTE. For the uncertainty analysis, a triangular distribution with bounds of $\pm 50\%$ was used for cost parameters and of $\pm 10\%$ for mortality. Data are from [8, 36, 37].

come countries, we estimated rates of rotavirus-associated hospitalization and outpatient visits on the basis of the approach described by Parashar et al [39]. Rotavirus-attributable hospitalizations and outpatient visits were estimated by multiplying the number of diarrhea-related hospitalizations and outpatient visits by the estimated proportion of diarrhea events attributable to rotavirus [39]. Estimates of rates of hospitalization and outpatient visits in upper-middle–income countries were based on pooled results of studies conducted in 6 countries in this income stratum [9–14]. The rate of outpatient visits was estimated to be 8 times that of hospitalization [8]. Annual rates were converted to 5-year cumulative rates.

Estimates of rotavirus mortality rate for each region-income group were calculated on the basis of the population-weighted mean of country-specific rates estimated by the WHO [1]. Rotavirus-associated hospitalizations and deaths were distributed into the following age categories based on a literature review of the age distribution of rotavirus-associated hospitalizations: 0–2 months, 3–5 months, 6–8 months, 9–11 months, 12–23 months, 24–35 months, 36–47 months, and 48–59 months [10, 11, 14, 40–65]. The distribution of outpatient visits was assumed to be the same.

The DALY burden from rotavirus mortality was calculated on the basis of the standardized life expectancy at 1 year of age. The DALYs from cases of rotavirus disease resulting in outpatient or hospital visits were calculated on the basis of default disability weights [66] and an estimated illness duration of 6 days [36]. To ensure comparability, DALY calculations included age weights and a discount rate of 3% [67].

Economic costs associated with rotavirus. The direct medical cost includes the costs of a visit or hospital stay and diagnostic tests and medications. Inpatient and outpatient visit costs were estimated using standardized unit costs from the WHO Choosing Interventions that are Cost Effective (CHOICE) project, which estimates per diem hospitalization costs and outpatient visit costs by geographical region and mortality stratum [36]. The published function was used to estimate country-specific hospital per diem costs for the present study. The mean hospital and outpatient unit cost of each regional income group was calculated by determining a population-weighted mean of the country-specific cost estimates. The mean length of hospital stay was estimated to be 4 days [9, 11, 14, 15–32]. Diagnostic and medication costs were estimated as a proportion of the per diem and per visit costs from studies in

10 countries [68, 69]. Transportation cost and productivity losses to care providers were estimated in the same manner. Cost estimates were converted from 2000 international dollars to 2007 US dollars with use of the Consumer Price Index [70], purchasing power parity, and official exchange rates [71].

Vaccination: effectiveness and costs. The vaccine evaluated was a live attenuated monovalent human rotavirus vaccine administered orally with the first and second doses of diphtheria, tetanus, and pertussis vaccine (DTP) at ~2 and ~4 months of age, respectively [34]. To estimate vaccination effectiveness, the model combined information on vaccine coverage, vaccine efficacy, and the relative coverage of children at high risk of infection. Vaccine coverage was based on DTP coverage (doses 1 and 2) for each age category with use of 17 demographic and health surveys conducted in low- and lower-middle–income countries [72]. Demographic and health survey estimates were similar to WHO–United Nations Children's Fund (UNICEF) best estimates for DTP coverage [37]. For the European region, WHO-UNICEF estimates for DTP coverage were used because of limited availability of DHS data, and it was assumed that vaccination occurred at the recommended time. Because few DHS data were available for upper-middle–income countries, vaccine timing and coverage were assumed to be the same as those in lower-middle–income countries.

Several studies suggest that infants who die of diarrhea are less likely to have access to routine vaccinations [62, 73–75]. The model assumed that children who would die of diarrhea in the absence of rotavirus vaccination have a lower level of vaccination coverage. For the base case, vaccination coverage among children at high risk of infection was assumed to be 90% (range, 50%–100%) that among children at low risk of infection.

Vaccine efficacy against severe rotavirus disease resulting in hospitalization was 85%, based on data from Latin America [33]. This efficacy was also assumed for mortality. Efficacy against outpatient visits was estimated as the mean efficacy reported for severe (85%) [33] and any (70%) [34] rotavirus gastroenteritis. The efficacy of receiving 1 dose was assumed to be 50% of that of a full course.

The cost of vaccination includes administration costs, the price of each dose, and expected losses from waste. Administration costs for the low- and lower-middle–income countries were estimated using the WHO Global Immunization Vision and Strategy costing model [76]. Costs for the upper-middle–income countries were assumed to be twice those for the lower-middle–income group for each region. Because the current and future price of rotavirus vaccines is currently unknown, the analysis used a price range of $2–$15 per 2-dose course. A 10% vaccine wastage rate was assumed. The cost of adverse events associated with vaccination was not included, because the vaccine has a safety profile equivalent to that of placebo [34].

Cost-effectiveness. The primary measures of cost-effectiveness in this study are the incremental cost per DALY averted and incremental cost per death averted. The incremental cost is the difference in the costs with and without vaccination (costs of vaccination minus the averted costs from prevented cases). The incremental cost-effectiveness ratio (ICER) is defined as the incremental costs divided by the difference in the DALYs (or deaths) with and without vaccination. Cost-effectiveness was assessed from the health care system perspective for comparability with other published studies. The break-even price, which is the price per vaccine dose at which the costs averted because of vaccination exactly offset the costs of vaccination, was calculated from the health care system and societal perspective.

Uncertainty and sensitivity analyses. One-way sensitivity analyses were completed by varying the individual values for key model inputs among a high, low, and baseline estimate. Variables included hospitalization, outpatient, and mortality rates; vaccine efficacy; relative coverage; and vaccine coverage. The model assumed that rotavirus vaccine coverage would be the same as current coverage and timing for DTP doses 1 and 2. Scenario analyses were conducted to consider on-time coverage, with children vaccinated at the recommended 2 and 4 months of age, and theoretical coverage, assuming both an optimistic level of coverage based on WHO-UNICEF best estimates of coverage [37] and on-time vaccine delivery.

A probabilistic sensitivity analysis was conducted to develop a range of estimates of burden and cost-effectiveness and to identify specific variables that have substantial influence on outcomes and that may merit additional data collection. A Monte Carlo simulation model was developed using distributions for key input variables. Multiple iterations (10,000) generated output distributions and uncertainty limits (5% and 95%) for key variables [77]. Contribution to variance analysis was conducted to determine which input variables contributed the most to the uncertainty in the outputs. Variables used in the model can be found in tables 1–3.

RESULTS

Health and economic burden. Annually, rotavirus accounts for 527,025 deaths and 147 DALYs per 1000 children in all countries included in this analysis (Table 3). Rotavirus-associated outpatient visits and hospitalizations result in direct medical treatment costs of $325 million ($202 million–$453 million) and total societal costs of $423 million ($262 million–$590 million) each year. In general, there is an inverse relationship between the health burden and economic burden of rotavirus, with health burden concentrated in low-income countries and the economic burden concentrated in upper-middle–income countries. There is also significant variation in

Table 3. Economic and Health Burden of Rotavirus Gastroenteritis by Region-Income Group (Cost per Annual Birth Cohort)

Region, income level	No. of medical visits	Medical cost		Societal cost		No. of deaths	DALYs per 1000 children
		1000 US$	US$ per child	1000 US$	US$ per child		
Africa							
Low	5,469,819	38,095	1.52	50,122	1.99	237,606	322
Lower-middle	408,373	3370	1.83	4386	2.38	1443	27
Upper-middle	30,636	426	3.64	548	4.68	141	41
All	5,908,828	41,891	1.55	55,056	2.03	239,190	300
Americas							
Low	91,635	794	1.89	1042	2.47	1736	140
Lower-middle	780,851	15,501	4.40	20,192	5.73	4682	45
Upper-middle	1,995,810	80,980	10.62	104,493	13.71	8197	37
All	2,868,296	97,275	8.41	125,727	10.87	14,615	43
Eastern Mediterranean							
Low	1,993,557	23,028	2.51	30,486	3.33	50,449	187
Lower-middle	1,275,197	20,420	3.55	26,683	4.64	10,111	60
Upper-middle	274,941	13,147	12.52	16,965	16.16	592	19
All	3,543,695	56,595	3.55	74,134	4.65	61,152	130
Europe							
Low	328,233	3624	2.40	4756	3.15	5392	122
Lower-middle	818,298	14,658	3.97	19,081	5.17	4555	42
Upper-middle	185,127	6802	9.62	8820	12.48	4	0
All	1,331,658	25,084	4.25	32,657	5.53	9951	57
Southeast Asia[a]							
Low	7,876,061	34,172	0.94	44,501	1.23	161,253	152
Lower-middle	311,986	3034	2.16	3933	2.79	1732	42
All	8,188,047	37,206	0.99	48,434	1.29	162,985	148
Western Pacific							
Low	558,083	4606	1.80	6021	2.35	8090	107
Lower-middle	4,596,693	59,937	2.89	77,653	3.74	30,890	51
Upper-middle	142,707	2802	5.14	3591	6.59	152	9
All	5,297,483	67,345	2.82	87,265	3.66	39,132	56
All regions							
Low	16,317,388	104,322	1.39	136,929	1.83	464,526	211
Lower-middle	8,191,397	116,920	3.16	151,929	4.11	53,413	49
Upper-middle	2,629,222	104,157	10.37	134,417	13.39	9086	31
All	27,138,006	325,400	2.67	423,275	3.47	527,025	147

NOTE. DALYs, disability-adjusted life-years.

[a] No upper-middle–income countries were identified in the Southeast Asian region.

the health and economic burden among countries in different geographic regions that fall into the same income category

Vaccine effectiveness and cost-effectiveness. With a national rotavirus vaccination program, an estimated 227,673 lives (209,000–266,000 lives) would be saved in low- and middle-income countries in each annual birth cohort (Table 4). In addition to improving health, vaccination would save $188 million ($121 million–$272 million) in treatment costs and $243 million ($157 million–$354 million) in total societal costs.

From the health care system perspective, vaccination would be cost-saving in lower-middle– and upper-middle–income regions for vaccine prices <$0.53 and <$2.00, respectively (break-even price). Vaccination would require a net financial investment at higher prices and at any price in the low-income region. At a vaccine price of $5 per dose, the ICER was $88 ($79–$126), $291 ($242–$402), and $329 ($173–$547) per DALY averted in the low-, lower-middle–, and upper-middle–income groups, respectively.

Table 5 shows the differences in benefits and cost-effectiveness of vaccination among regions and income groups. In low-income countries, vaccination would result in a smaller percentage reduction in rotavirus-associated deaths and medical

Table 4. Costs, Benefits, and Cost-Effectiveness of Rotavirus Vaccination by Income Group

Variable	Income group: Lower	Lower-middle	Upper-middle	All
Total medical cost				
Without vaccine	104,322,143	116,920,464	104,157,303	325,399,910
With vaccine	58,988,917	41,230,798	37,225,355	137,445,070
Averted	45,333,226	75,689,666	66,931,948	187,954,840
Percent reduction	0.43	0.65	0.64	0.58
Total societal costs averted	59,178,616	97,921,712	85,991,851	243,092,179
Cost of vaccination				
$1/dose	162,294,905	109,857,673	46,436,100	318,588,677
$2/dose	275,851,447	182,831,561	66,912,285	525,595,293
$3/dose	389,407,989	255,805,449	87,388,470	732,601,908
$5/dose	616,521,073	401,753,224	128,340,841	1,146,615,138
$7.50/dose	900,412,428	584,187,944	179,531,305	1,664,131,676
Medical break-even price	−0.03	0.53	2.00	0.37
Societal break-even price	0.09	0.84	2.93	0.64
DALYs				
Without vaccine	15,827,898	1,827,512	311,876	17,967,286
With vaccine	9,372,297	706,807	125,357	10,204,462
DALYs averted	6,455,601	1,120,705	186,519	7,762,825
No. of deaths				
Without vaccine	464,526	53,413	9086	527,025
With vaccine	275,057	20,645	3650	299,352
Averted	189,469	32,768	5436	227,673
Cost-effectiveness, US$ per DALY				
$1/dose	18	30	Cost-saving	17
$2/dose	36	96	Cost-saving	43
$3/dose	53	161	110	70
$5/dose	88	291	329	123
$7.50/dose	132	454	604	190
Cost-effectiveness, US$/death				
$1/dose	617	1043	Cost-saving	574
$2/dose	1217	3270	Cost-saving	1483
$3/dose	1816	5497	3763	2392
$5/dose	3015	9951	11,296	4211
$7.50/dose	4513	15,518	20,713	6484

NOTE. DALYs, disability-adjusted life-years.

visits, particularly in Africa and the eastern Mediterranean region (35%). The lower percentage reductions are attributable to lower coverage rates and greater delays in vaccination in these regions. Nevertheless, vaccination would be most cost-effective in these same low-income countries because of the higher overall rotavirus-associated mortality rates.

Sensitivity and uncertainty. Table 6 shows the results of the 1-way sensitivity analysis for individual variables and their contribution to variance in the probabilistic sensitivity analysis. Results are shown for ICER at $5 per dose for each income level. The contribution to variance shows the proportion of overall uncertainty in cost-effectiveness attributable to the individual variable in the probabilistic model.

In low- and lower-middle–income regions, 3 variables contribute the majority of uncertainty to the estimate of cost-effectiveness: vaccine efficacy against rotavirus-associated mortality, rotavirus-associated mortality rate, and relative vaccination coverage among children at the highest risk of rotavirus-associated mortality, compared with children at lower risk. In both income groups, vaccine efficacy contributes over one-half of the overall uncertainty. In the low-income region, economic variables have little effect on overall uncertainty. In lower-middle– and upper-middle–income regions, economic variables, including hospital and outpatient visit costs, contribute more to overall uncertainty regarding cost-effectiveness.

Table 7 shows the estimated impact and cost-effectiveness of

Table 5. Benefits and Cost-Effectiveness of Rotavirus Vaccination by Region and Income Group

Region, income group	No. (%) of medical visits averted	Medical costs averted		Societal costs averted		No. (%) of deaths averted	Cost-effectiveness by vaccine price (US$/dose), US$/DALY			
		1000 US$ (2007)	Percentage	1000 US$ (2007)	Percentage		$1	$2	$5	$7.50
Africa										
Low	1,928,025 (35)	13,944	37	18,264	36	83,950 (35)	13	25	61	91
Lower-middle	274,149 (67)	2353	70	3049	70	958 (66)	95	211	561	852
Upper-middle	20,612 (67)	299	70	383	70	94 (66)	47	123	351	541
All	2,222,785 (38)	16,597	40	21,696	39	85,001 (36)	13	27	67	100
Americas										
Low	49,095 (54)	442	56	577	55	927 (53)	24	48	122	184
Lower-middle	468,339 (60)	9664	62	12,532	62	2774 (59)	19	95	321	510
Upper-middle	1,199,654 (60)	50,709	63	65,139	62	4857 (59)	…[a]	…[a]	274	506
All	1,717,088 (60)	60,816	63	78,248	62	8558 (59)	22	44	109	163
Eastern Mediterranean										
Low	702,697 (35)	8404	36	11,077	36	17,824 (35)	21	42	104	156
Lower-middle	856,065 (67)	14,231	70	18,512	69	6712 (66)	25	77	234	364
Upper-middle	184,975 (67)	9217	70	11,839	70	393 (66)	…[a]	…[a]	340	743
All	1,743,737 (49)	31,851	56	41,428	56	24,929 (41)	17	49	143	222
Europe										
Low	221,525 (67)	2538	70	3316	70	3611 (67)	35	60	136	199
Lower-middle	550,786 (67)	10,261	70	13,297	70	3037 (67)	56	129	348	531
Upper-middle	129,686 (70)	4955	73	6395	73	3 (69)	…[a]	6647	27,602	45,065
All	901,997 (68)	17,754	71	23,008	70	6651 (67)	44	98	259	393
Southeast Asian										
Low	3,902,554 (50)	17,631	52	22,857	51	79,184 (49)	22	44	109	163
Lower-middle	186,269 (60)	1888	62	2436	62	1024 (59)	40	117	348	540
All	4,088,823 (50)	19,519	52	25,292	52	80,208 (49)	23	45	112	168
Western Pacific										
Low	276,528 (50)	2373	52	3087	51	3973 (49)	20	51	142	219
Lower-middle	2,744,419 (60)	37,293	62	48,097	62	18,262 (59)	26	90	280	439
Upper-middle	85,388 (60)	1752	63	2236	62	90 (59)	7	339	1336	2167
All	3,106,334 (59)	41,418	62	53,420	61	22,324 (57)	25	84	260	407
All regions										
Low	7,080,424 (43)	45,333	43	59,179	43	189,469 (41)	18	36	88	132
Lower-middle	5,080,027 (62)	75,690	65	97,922	64	32,768 (61)	30	96	291	454
Upper-middle	1,620,314 (62)	66,932	64	85,992	64	5436 (60)	…[a]	…[a]	329	604
All	13,780,765 (51)	187,955	58	243,092	57	227,673 (43)	17	43	123	190

[a] Vaccination is cost saving at this price.

Table 6. Sensitivity and Uncertainty Analysis: Best and Worst Case Estimates of Cost-Effectiveness for Individual Variables (1-Way Sensitivity Analysis) and Overall Contribution to Variance (Probabilistic Analysis)

	Cost-effectiveness, US$/DALY at $5/dose								
	Low income			Lower-middle income			Upper-middle income		
Variable	Worst	Best	Contribution to variance, %	Worst	Best	Contribution to variance, %	Worst	Best	Contribution to variance, %
Vaccine efficacy against mortality	122	82	65.9	386	261	55.7	449	305	12.4
Relative immunization coverage of children at high risk of infection	103	88	16.7	326	279	13.6	380	325	2.8
Rotavirus-associated mortality rate	100	87	12.3	317	276	9.6	369	322	1.7
Vaccination program cost	96	91	1.7	305	285	2.0	389	299	6.3
Outpatient visit treatment cost	95	91	1.0	310	280	5.6	420	268	19.4
Hospital visit treatment cost	95	91	1.2	313	277	8.4	448	240	37.3
1-dose efficacy	94	92	<1	298	292	<1	351	337	<1
Vaccine efficacy for outpatient visits	94	92	<1	305	289	1.4	394	313	4.7
Vaccine efficacy for hospital visits	94	93	<1	303	290	<1	393	317	4.0
Outpatient visit rate	94	92	<1	300	290	<1	370	318	2.2
Hospital visit rate	94	93	<1	301	289	1.0	380	309	4.7
Length of hospital stay	94	93	<1	301	289	1.0	379	309	4.5

NOTE. Ranges and distribution of individual variables are shown in table 1.

vaccination for the 3 immunization scenarios examined: current timing, on-time, and theoretical (on-time and increased coverage). On-time immunization would increase the impact of vaccination on mortality, particularly in low-income regions. In the low-income countries in Africa, it would increase mortality reduction by one-third and reduce the cost-effectiveness ratio by 25%. The theoretical immunization scenario would result in further increases in mortality reduction but no changes in cost-effectiveness.

DISCUSSION

Rotavirus gastroenteritis annually results in 27 million hospital and outpatient visits and 527,000 deaths among children <5 years of age in developing countries, at an estimated treatment cost of $325 million and total societal costs of $423 million. Assuming current vaccination coverage and timing, the integration of a rotavirus vaccine into national vaccination programs could prevent an estimated 227,000 deaths, 13.8 million medical visits, and 7.8 million DALYs, saving $188 million in treatment costs and $243 million in total costs. Vaccination would not be cost-saving at most of the prices considered in this analysis. However, the World Health Report (from 2002) suggests that interventions are very cost-effective if the ICER is less than the country's per capita gross domestic product and are cost-effective if the ICER is <3 times the per capita gross domestic product [78]. With use of these standards, rotavirus vaccination is very cost-effective in all income groups for a range of vaccine prices evaluated in the analysis.

The value of rotavirus vaccination as a health investment also depends on the other interventions available for improving child health and the availability of financial resources. On the basis of WHO-CHOICE, point-of-use water disinfection with education is the most cost-effective water and sanitation intervention in most regions, ranging from $161 per DALY in countries in Africa with high mortality to $1092 per DALY in countries in Latin America with low mortality. Introduction of expanded oral rehydration therapy coverage to 50% as a part of supplementation interventions had an ICER of <$25 per DALY in Africa and >$1200 per DALY in Latin America [79]. These comparisons suggest that rotavirus vaccination could be as cost-effective as other interventions for prevention or treatment of diarrhea, depending on vaccine price. However, differences in the nature of these interventions and the lack of empirical, directly compared cost-effectiveness trials limit the comparability of these results.

Three factors that greatly affected the estimated performance of a rotavirus vaccination program were the timing of vaccine delivery, the overall vaccine coverage, and the relative vaccine coverage among children who die of rotavirus, compared with all children. If a rotavirus vaccine was delivered on time at the age of 2 and 4 months and without the delays assumed in the model, an additional 46,000 rotavirus deaths (total of 274,000 deaths) could be averted. Improving vaccination coverage to the 90th percentile of coverage for each region and income level and optimizing timing of vaccine delivery could prevent an additional 125,978 deaths, compared with current vaccination practices. In low-income countries, vaccination would prevent 41% of rotavirus-related deaths with the current timing and coverage, compared with 67% with optimal levels.

The sensitivity analyses identified several factors that are

Table 7. Rotavirus Vaccination Impact and Cost-Effectiveness (at US$5/dose) by Immunization Scenario and Region-Income Group

	Current vaccination			On-time			Theoretical		
Region, income group	No. of deaths averted	Reduction, %[a]	US$/DALY	No. of deaths averted	Reduction, %[a]	US$/DALY	No. of deaths averted	Reduction, %[a]	US$/DALY
Africa									
Low	83,950	35	61	112,856	47	47	158,269	67	47
Lower-middle	958	66	561	995	69	551	1019	71	551
Upper-middle	94	66	351	97	69	344	100	71	344
Americas									
Low	927	53	122	1111	64	107	1156	67	107
Lower-middle	2774	59	321	3169	68	279	3306	71	279
Upper-middle	4857	59	274	5548	68	216	5787	71	216
Eastern Mediterranean									
Low	17,824	35	104	23,962	47	80	33,604	67	80
Lower-middle	6712	66	234	6973	69	229	7139	71	229
Upper-middle	393	66	340	408	69	325	418	71	325
Europe									
Low	3611	67	136	3611	67	136	3695	69	136
Lower-middle	3037	67	348	3037	67	348	3216	71	348
Upper-middle	3	69	27,602	3	69	27,602	3	71	27,602
Southeast Asia									
Low	79,184	49	109	86,940	54	102	107,410	67	102
Lower-middle	1024	59	348	1091	63	329	1223	71	329
Western Pacific									
Low	3973	49	142	4362	54	133	5389	67	133
Lower-middle	18,262	59	280	19,452	63	264	21,809	71	264
Upper-middle	90	59	1336	96	63	1,247	107	71	1,247
All regions									
Low	189,469	41	88	232,841	50	75	309,524	67	75
Lower-middle	32,768	61	291	34,717	65	278	37,712	71	278
Upper-middle	5436	60	329	6152	68	274	6415	71	274

[a] Compared with baseline.

likely to influence the actual impact and cost-effectiveness of vaccination. In low-income regions, the effectiveness of vaccination will be affected by the efficacy of vaccination in those settings and the ability of vaccination to reach children at high risk of infection on time. Several studies have identified a relationship between immunization status and mortality, which suggests that infants who have been vaccinated are less likely to die than are infants who are not fully immunized [62, 73–75]. If those who die are less likely to have been vaccinated, the effectiveness (and cost-effectiveness) of vaccination will be reduced. Targeted efforts to increase the coverage of children at the greatest risk of mortality could improve the impact of vaccination programs.

Several limitations of this study should be considered in the interpretation of the findings. First, estimates of health burden and the impact of vaccination were based on a limited number of publications that may not be generalizable to all countries within income-region strata. Second, there are few empirical data on resource use and cost for rotavirus gastroenteritis, particularly in developing countries. For this reason, a standardized approach developed by the WHO for its WHO-CHOICE project was used. Additional information on treatment and societal costs may provide additional information on the economic benefits of vaccination and potential cost offsets. Third, vaccine price has a significant influence on the cost-effectiveness of vaccination, but precise information on current and future costs are not available. Additional analyses are needed to explore the effect of likely prices on vaccine introduction and cost-effectiveness. Finally, potential herd immunity of rotavirus vaccination was not factored into our analysis; however, any herd immunity effects of rotavirus vaccination would only improve the overall cost-effectiveness of vaccination.

In conclusion, our findings indicate that vaccination can effectively reduce the tremendous health and economic burden of rotavirus gastroenteritis. Timing of vaccination, vaccination coverage, and the ability of vaccination programs to reach children at risk of death due to rotavirus disease will substantially impact the effectiveness of vaccination. Although rotavirus vaccination is unlikely to be cost-saving from the health care perspective at the prices considered, vaccination is cost-effective across a range of prices using several standards. Compared with other interventions to reduce diarrhea-associated mortality, the benefits of rotavirus vaccination may be achieved quickly because of the ability of the vaccine to be incorporated into existing immunization programs and the short time between vaccination and averted mortality. Although rotavirus vaccination may be considered to be cost-effective, it will require an investment of resources to procure and deliver the vaccine, the magnitude of which is determined by vaccine price. Although some of these costs will be defrayed by averted medical costs, additional national or international resources will likely be needed to bring vaccines to children in the poorest countries who need them the most. In the short term, external resources may be available from international donors, such as funding from the GAVI Alliance for eligible low-income countries; however, countries will need to identify internal resources for rotavirus vaccination program sustainability.

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